AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

These amendments introduce no new matter and support for the changes is replete throughout the specification, claims, and drawings as originally filed. All changes are made without prejudice and are not to be construed as abandonment of any previously claimed subject matter or agreement with any objection or rejection of record.

Listing of Claims:

1. (**Currently Amended**) A computer-implemented method for characterizing an interrogation position in nucleic acid segments collected from a case group **of n individuals** and a control group **of m individuals**, wherein the interrogation position contains a biallelic polymorphism, comprising:

collecting a first pooled sample by pooling biological samples from individuals in the case group, wherein n is an integer equal to or larger than 2, and wherein individuals in the case group are selected based on presence of a phenotypic characteristic of interest;

collecting a second pooled sample by pooling biological samples from individuals in the control group, wherein m is an integer equal to or larger than 2, and wherein individuals in the control group are selected based on lack of the phenotypic characteristic of interest;

determining a first measure of relative allele frequency at the interrogation position in the first pooled sample, wherein the first measure of relative allele frequency is derived from intensity signals from a first probe set;

determining a second measure of relative allele frequency at the interrogation position in the second pooled sample, wherein the second measure of relative allele frequency is derived from intensity signals form a second probe set;

inputting into a computer system [[a]] **the** first measure of relative allele frequency ~~**at the interrogation position in a nucleic acid segment derived from a first sample collected from the**~~

~~case group of n individuals, wherein n is an integer equal to or larger than 2, and wherein individuals in the case group are selected based on a phenotypic characteristic of interest~~;

inputting into the computer system **[[a]]** **the** second measure of relative allele frequency ~~at the interrogation position in a nucleic acid segment derived from a second sample collected from the control group of m individuals, wherein m is an integer equal to or larger than 2, and wherein individuals in the control group are selected based on lack of the phenotypic characteristic of interest~~;

analyzing in the computer system the first measure and the second measure to characterize the interrogation position; and

outputting a result of said analyzing, wherein the result characterizes the interrogation position as being associated with the phenotypic characteristic of interest.

2. (**Cancelled**)

3. (**Previously Presented**) The method of claim 1, wherein the individuals in the case and control groups are animals.

4. (**Previously Presented**) The method of claim 1, wherein the individuals in the case and control groups are mammals.

5. (**Previously Presented**) The method of claim 1, wherein the individuals in the case and control groups are humans.

6. (**Cancelled**)

7. (**Previously Presented**) The method of claim 1, wherein the phenotypic characteristic of interest is susceptibility or resistance to a disease, a disorder, or infection of a pathogen.

8. (**Previously Presented**) The method of claim 1, wherein the phenotypic characteristic of interest is susceptibility or resistance to effects of uptake of food or drink.

9. **(Original)** The method of claim 8, wherein the drink is an alcoholic drink.

10. **(Previously Presented)** The method of claim 1, wherein the phenotypic characteristic of interest is susceptibility to, resistance to, or adverse effects of a therapy using a therapeutic agent or a medical device.

11. **(Currently Amended)** The method of claim 1, wherein **the** phenotypic characteristic of interest is selected from the group consisting of cancer, hematological disorders, autoimmune diseases, inflammatory diseases, cardiovascular diseases, liver diseases, neurodegenerative diseases, diabetes, kidney disorder, gastrointestinal disorders, pain, bacterial infection, parasitic infection, viral infection, and a specific stage of development thereof.

12. **(Previously Presented)** The method of claim 1, wherein the number of individuals in the case group, n, and the number of the individuals in the control group, m, are each larger than 5.

13. **(Previously Presented)** The method of claim 1, wherein the number of individuals in the case group, n, and the number of the individuals in the control group, m, are each larger than 100.

14. **(Previously Presented)** The method of claim 1, wherein the number of individuals in the case group, n, and the number of the individuals in the control group, m, each independently varies between 10 and 100,000.

15. **(Previously Presented)** The method of claim 1, wherein the interrogation position is a SNP position.

16. **(Previously Presented)** The method of claim 15, wherein a genetic region containing the SNP position was not previously known to be associated with the phenotypic characteristic of interest.

17. **(Cancelled)**

18. **(Currently Amended)** The method of claim **[[17]]** **1**, wherein the biological samples are pooled by combining a substantially equal amount of biological sample from each individual in each group.

19. **(Currently Amended)** The method of claim **[[17]]** **1**, wherein the biological samples are selected from the group consisting of genomic DNA, mitochondrial DNA, extragenomic DNA, cDNA, and RNA.

20. (**Currently Amended**) The method of claim **[[17]]** **1**, wherein the biological samples from the case group and the control group are labeled with a detectable marker.

21. **(Original)** The method of claim 20, wherein the detectable marker is selected from the group consisting of cychrome, fluorescein, Alexa-488, radioisotopes, and biotin.

22. (**Previously Presented**) The method of claim 1, wherein the first sample is collected by pooling genetic material from the case group of individuals and amplifying the pooled genetic materials from the case group and the second sample is collected by pooling genetic material from the control group of individuals and amplifying the pooled genetic materials from the control group.

23. (**Previously Presented**) The method of claim 22, wherein amplicons of genetic material from the case group are labeled with a different detectable marker than are amplicons of genetic material from the control group.

24. (**Previously Presented**) The method of claim 23, wherein amplicons of genetic materials from the case group are each labeled with biotin; and amplicons of genetic materials from the control group are each labeled with fluorescein.

25. **(Original)** The method of claim 23, wherein the first sample and second sample are mixed after being labeled, followed by hybridization to an array and subsequent staining, wherein said first sample is stained with different stain than said second sample.

26. (**Previously Presented**) The method of claim 1, wherein the first sample is collected by amplifying genetic material from each individual in the case group of individuals and then pooling the amplified genetic materials from all of the individuals in the case group, and the second sample is collected by amplifying genetic material from each individual in the control group of individuals and then pooling the amplified genetic materials from all of the individuals in the control group.

27. (**Cancelled**)

28. **(Original)** The method of claim 1, wherein the first measure of relative allele frequency is derived from a first measure of intensity of signals from a first probe set on a first oligonucleotide array; and the second measure of relative allele frequency is derived from a second measure of intensity of signals from a second probe set on the first or a second oligonucleotide array.

29. (**Previously Presented**) The method of claim 28, wherein the density of the oligonucleotide array is at least 100 probes per square centimeter.

30. (**Previously Presented**) The method of claim 28, wherein the density of the oligonucleotide array is at least 1000 probes per square centimeter.

31. (**Previously Presented**) The method of claim 28, wherein the density of the oligonucleotide array is between 100-100,000,000 probes per square centimeter.

32. (**Previously Presented**) The method of claim 28, wherein the density of the oligonucleotide array is between 1,000,000-80,000,000 probes per square centimeter.

33. **(Original)** The method of claim 28, wherein each of the oligonucleotides on the array is 10-100 nucleotides in length.

34. **(Original)** The method of claim 28, wherein each of the oligonucleotides on the array is 20-50 nucleotides in length.

35. **(Original)** The method of claim 28, further comprising:

correcting the first and second measures of intensity.

36. **(Original)** The method of claim 35, wherein the step of correcting includes subtracting a background intensity.

37. **(Original)** The method of claim 36, wherein the background intensity is the intensity of a probe cell having the 1000^{th} lowest intensity on the oligonucleotide array.

38. **(Original)** The method of claim 36, wherein the background intensity is determined by calculating an equation of the form:

$$\frac{<I_R^{mm}>+<I_A^{mm}>}{2}.$$

39. **(Original)** The method of claim 28, further comprising:

evaluating the first and second measures of intensity to determine whether the first probe set and the second probe set have each detected the nucleotide sequences that they were designed to detect.

40. **(Original)** The method of claim 39, wherein the step of evaluating includes determining if the measure of intensity of a perfectly complementary probe in the first probe set is greater than any of the measures of intensity of mismatch probes in the first probe set, in which case the first probe set is a conforming probe set; and determining if the measure of intensity of a perfectly complementary probe in the second probe set is greater than any of the measures of intensity of mismatch probes in the second probe set, in which case the second probe set is a conforming probe set

41. **(Original)** The method of claim 28, wherein the first or second probe set is included in a probe tiling that comprises

a reference tiling comprising a set of reference oligonucleotide probes with a varying nucleotide at the interrogation position and a set of complementary reference oligonucleotide probes that are each complementary to the corresponding reference oligonucleotide probes; and

an alternate tiling comprising a set of alternate oligonucleotide probes with a varying nucleotide at the interrogation position and a set of complementary alternate oligonucleotide probes that are each complementary to the corresponding alternate oligonucleotide probes.

42. **(Original)** The method of claim 41, wherein the reference and alternate oligonucleotide probes differ from each other by a nucleotide at the interrogation position.

43. **(Original)** The method of claim 41, wherein the varying nucleotide at the interrogation position is A, T, G, U or C.

44. **(Original)** The method of claim 43, further comprising:

calculating a number of conforming probe sets for the reference tiling;

calculating a total number of probe sets in the reference tiling;

calculating a conformance value for the reference tiling by dividing the number of conforming probe sets with the total number of probe sets in the reference tiling;

calculating a number of conforming probe sets for the alternate tiling;

calculating a total number of probe sets in the alternate tiling; and

calculating a conformance value for the alternate tiling by dividing the number of conforming probe sets with the total number of probe sets in the alternate tiling.

45. **(Original)** The method of claim 44, further comprising:

discarding any measure of intensity obtained from the tiling that has the conformance value lower than 0.6.

46. **(Original)** The method of claim 44, further comprising:

discarding any measure of intensity obtained from the tiling that has the conformance value lower than 0.9.

47. **(Original)** The method of claim 28, wherein said first probe set and said second probe set are the same probe set.

48. **(Previously Presented)** The method of claim 1, wherein relative allele frequency is based on variation of a nucleotide at the interrogation position of the nucleic acid segments relative to a reference nucleic acid segment, the nucleotide at said interrogation position in said reference nucleic acid segment being designated a reference allele and a nucleotide at said interrogation position that differs from said reference allele being designated an alternate allele; and the measure of relative allele frequency is the proportion of either said reference allele or said alternate allele at the interrogation position.

49. **(Original)** The method of claim 48, wherein the relative allele frequency is determined by calculating an equation of the form:

$c_r/(c_a + c_r)$ or

$c_a/(c_a + c_r)$,

where c_r is the concentration of the reference allele and c_a is the concentration of the alternate allele.

50. **(Withdrawn)** The method of claim 48, wherein the measure of relative allele frequency is determined by calculating an equation of the form:

$I_R/(I_A + I_R)$ or

$I_A/(I_A + I_R)$,

where I_R is an intensity of signal from the reference allele, and I_A is an intensity of signal from the alternate allele.

51. **(Withdrawn)** The method of claim 48, wherein the measure of relative allele frequency is determined using measurements of hybridization to perfect match probes.

52. **(Previously Presented)** The method of claim 48, wherein relative allele frequency is determined using at least two intensity of signal measurements by calculating at least one of the equations of the form:

$<I_R>/(<I_A> + <I_R>)$ and

$<I_A>/(<I_A> + <I_R>)$,

where $<I_R>$ is an average of intensities of signal measurements from the reference allele, and $<I_A>$ is an average of intensities of signal measurements from the alternate allele.

53. **(Withdrawn)** The method of claim 52, wherein the averages of intensities of signal measurements are arithmetic means of intensities of signal measurements.

54. **(Original)** The method of claim 52, wherein the averages of intensities of signal measurements are trimmed means of intensities of signal measurements.

55. **(Withdrawn)** The method of claim 48, wherein each measure of relative allele frequency is determined using at least two intensity of signal measurements by calculating at least one of the equations of the form:

$$< I_R/(I_A + I_R) > = \frac{\sum_{i=1}^{n}\left(\frac{I_R}{I_A+I_R}\right)_i}{n} \text{ and}$$

$$<I_A/(I_A + I_R)> = \frac{\sum_{i=1}^{n}\left(\frac{I_A}{I_A+I_R}\right)_i}{n},$$

where I_R is an intensity of signal measurement from the reference allele, I_A is an intensity of signal measurement from the alternate allele, $< I_R/(I_A + I_R)>$ and $<I_A/(I_A + I_R)>$ are averages of the ratios of intensities of signal measurements, and n is a number of offsets at which the intensity of signal measurements were measured.

56. **(Withdrawn)** The method of claim 55, wherein the averages of the ratios of intensities of signal measurements are arithmetic means of the ratios of intensities of signal measurements.

57. **(Withdrawn)** The method of claim 55, averages of the ratios of intensities of signal measurements are trimmed means of the ratios of intensities of signal measurements.

58. **(Withdrawn)** The method of claim 48, wherein wherein each measure of relative allele frequency is determined using at least one intensity of signal measurement that has been corrected.

59. **(Withdrawn)** The method of claim 58, wherein the at least one intensity of signal measurement is corrected by subtracting background.

60. **(Withdrawn)** The method of claim 59, wherein the background is calculated at least from intensity of signal measurements from mismatch probes.

61. **(Withdrawn)** The method of claim 60, wherein the background is calculated from a mean of the intensity of signal measurements from mismatch probes.

62. **(Withdrawn)** The method of claim 61, wherein the mean of intensities of signal measurements from mismatch probes is an arithmetic mean.

63. **(Withdrawn)** The method of claim 61, wherein the mean of intensities of signal measurements from mismatch probes is a trimmed mean.

64. **(Original)** The method of claim 1, wherein the step of analyzing the first measure and the second measure includes determining a difference between the first measure and the second measure.

65. **(Original)** The method of claim 64, further comprising:

determining if the difference falls within a predetermined percentile of a distribution of differences between first measures and second measures.

66. **(Original)** The method of claim 65, wherein the percentile of distribution is top 20%.

67. **(Original)** The method of claim 65, wherein the percentile of distribution is top 5%.

68. **(Previously Presented)** The method of claim 1, further comprising:

inputting into the computer system another first measure of relative allele frequency that is obtained by repeating the measurement of the first measure of relative allele frequency; and

inputting into the computer system another second measure of relative allele frequency that is obtained by repeating the measurement of the second measure of relative allele frequency, wherein the step of analyzing includes determining, based on the variation in the first measure and said another first measure and the variation in the second measure and said another second measure, whether the first, another first, second and another second measures of relative allele frequency are suitable for use in characterizing the interrogation position.

69. **(Previously Presented)** The method of claim 1, wherein the interrogation position is a SNP position at position i within a haplotype block having N different haplotype patterns, and each of the first and second measures of relative allele frequency is corrected by solving a first equation:

$$P_i \approx \sum_{j=1}^{N} m_{ij} f_j$$

where P_i is a corrected relative allele frequency of the interrogation position; N is the total number of different haplotype patterns within the haplotype block; m_{ij} is a coefficient having a value of +1 if the allele at position i in haplotype pattern j matches a reference allele of the SNP and having a value of 0 if the allele at position i matches an alternate allele of the SNP; and f_j is a haplotype pattern frequency.

70. **(Previously Presented)** The method of claim 69, wherein the corrected relative allele frequency, P_i, is constrained by a second equation:

$$\sum_{j=1}^{N} f_j = 1.$$

71. **(Original)** The method of claim 70, wherein the f_j has a value ranging from 0 to 1.

72. **(Original)** The method of claim 1, further comprising:

calculating a difference between the first measure of relative allele frequency and the second measure of relative allele frequency.

73. **(Original)** The method of claim 72, wherein the interrogation position is a SNP position at position i within a haplotype block having N different haplotype patterns, and the difference between the first measure and second measure of relative allele frequency is corrected by applying a third equation:

$$\Delta P_i \approx \sum_{j=1}^{N} m_{ij} \Delta f_j$$

where ΔP_i is a corrected relative allele frequency difference of the interrogation position; N is the total number of different haplotype patterns within the haplotype block; m_{ij} is a coefficient having a value of +0.5 if the allele at position i matches a reference allele of the SNP and having a value of -0.5 if the allele at position i matches an alternate allele of the SNP; and Δf_j is a haplotype pattern frequency difference.

74. **(Original)** The method of claim 73, wherein the third equation is constrained by a fourth equation:

$$\sum_{j=1}^{N} \Delta f_j = 0.$$

75. (**Previously Presented**) The method of claim 1, wherein the step of inputting the first measure includes inputting a plurality of first measures, and the step of inputting the second measure includes inputting a plurality of second measures.

76. **(Previously Presented)** The method of claim 75, wherein the plurality of first measures and the plurality of second measures correspond to duplicated or replicated measurements of the interrogation position in the nucleic acid segments.

77. **(Original)** The method of claim 1, wherein said interrogation position is a plurality of interrogation positions in the same or different nucleic acid segments, and for each interrogation position a said first measure of allele frequency and a said second measure of allele frequency are inputted into said computer system and analyzed to characterize said each interrogation position.

78. **(Original)** The method of claim 75, wherein the step of analyzing includes pairing a measure from the plurality of first measures and a measure from the plurality of the second measures based on common experimental conditions.

79. **(Original)** The method of claim 75, wherein the step of analyzing includes analyzing using a set of differences of paired measures using a method selected from the group comprising: a paired t-test; calculating an Olympic average; determining the median value; and all members of the set having the same sign.

80. **(Original)** The method of claim 75, where the step of analyzing includes calculating the mean of the plurality of first measures and the mean of the plurality of second measures.

81. **(Original)** The method of claim 80, further comprising:

analyzing the absolute difference between the mean of the plurality of first measures and the mean of the plurality of second measures by thresholding the difference between the means, wherein if the absolute difference between the mean of the plurality of first measures and the mean of the plurality of second measures is equal to or above the threshold value, the interrogation position is characterized as being associated with the phenotypic characteristic of interest.

82. **(Original)** The method of claim 81, wherein the threshold value is 0.04.

83. **(Original)** The method of claim 81, wherein the threshold value is 0.1.

84. **(Previously Presented)** The method of claim 81, further comprising:

inputting another plurality of first measures and another plurality of second measures;

calculating a mean of said another plurality of first measures and a mean of said another plurality of second measures;

analyzing the difference between the mean of said another plurality of first measures and the mean of said another plurality of second measures by using another threshold value.

85. **(Previously Presented)** The method of claim 84, wherein the threshold value is 0.05 and said another threshold value is 0.10, wherein if the absolute difference between the mean of said another plurality of first measures and the mean of said another plurality of second measures is equal to or above said another threshold value, the interrogation position is characterized as being associated with the phenotypic characteristic of interest.

86. **(Original)** The method of claim 75, wherein the step of analyzing includes:

calculating the standard deviation of the plurality of first measures and the standard deviation of the plurality of second measures; and

analyzing each of the standard deviations of the first and second pluralities of measures.

87. **(Original)** The method of claim 86, wherein each of the standard deviations of the first and second pluralities of measures is analyzed by using a chi-squared distribution to determine at least one cutoff value for the standard deviations.

88. **(Original)** The method of claim 87, further comprising:

discarding the plurality of the first or second measures if the calculated standard deviation of the plurality of the first or second measures is greater than the cutoff value.

89. **(Original)** The method of claim 75, further comprising:

calculating an arithmetic mean and standard deviation of the plurality of the first measures, and an arithmetic mean and standard deviation of the plurality of second measures, and

applying a t-test using said arithmetic means and standard deviations to determine whether it is likely that the plurality of first measures and the plurality of second measures are from the same or different distributions, where if the plurality of first measures and the plurality of second measures are found likely to be from different distributions, the interrogation position in the nucleic acid segment is characterized as being associated with the phenotypic characteristic of interest.

90. **(Original)** The method of claim 75, further comprising:

calculating an arithmetic mean and standard deviation for the plurality of the first measures, and an arithmetic mean and standard deviation for the plurality of second measures,

determining a distribution for the plurality of first measures based on said arithmetic mean and standard deviation of the plurality of first measures,

determining a distribution for the plurality of second measures based on said arithmetic mean and standard deviation of the plurality of second measures, and

determining a difference between said distribution for the plurality of first measures and said distribution for the plurality of second measures, wherein if the difference between said distribution of the plurality of first measures and said distribution of the plurality of second measures is significant, either positive or negative, the interrogation position in the nucleic acid segment is characterized as being associated with the phenotypic characteristic of interest.

91. **(Original)** The method of claim 89, wherein the likelihood that the plurality of first measures and the plurality of second measures are from different distributions is assessed by using a formula of the form:

$$t = \frac{< P'_1 > - < P'_2 >}{\sqrt{\frac{\sigma_1^2}{N_1} + \frac{\sigma_2^2}{N_2}}}$$

where t is the t-statistic in the t-test analysis; $<P'_1>$ and $<P'_2>$ are arithmetic means of the pluralities of first and second measures, respectively; σ_1 and σ_2 are standard deviations of the pluralities of

first and second measures, respectively; and N_1 and N_2 are numbers of members of the pluralities of first and second measures, respectively.

92. (**Previously Presented**) The method of claim 91, further comprising:

comparing the t-statistic with a Student t-distribution using a number of degrees of freedom, which is calculated by using an equation of the form $(N_1 + N_2 - 2)$, to obtain a p-value, where if the p-value is lower than 0.05, the interrogation position in the nucleic acid segment is characterized as being associated with the phenotypic characteristic of interest.

93. (**Previously Presented**) The method of claim 92, further comprising:

repeating the same steps for characterization of the interrogation position in the nucleic acid segment on one or more additional interrogation positions in the same or different nucleic acid segment;

discarding the interrogation positions having p-values higher than a cutoff value, and characterizing the remaining interrogation position(s) as being associated with the phenotypic characteristic of interest.

94. **(Original)** The method of claim 75, further comprising:

calculating absolute values of the plurality of the first measures and calculating absolute values of the plurality of the second measures;

ranking the absolute values of the plurality of the first measures; ranking the absolute values of the plurality of the second measures; and

determining the rank-sum distribution for both the plurality of the first measures and the plurality of the second measures.

95. **(Original)** The method of claim 94, wherein the rank-sum distribution is determined by using a Wilcoxson rank-sum test.

96. **(Original)** The method of claim 95, further comprising:

determining the p-value for the interrogation position, wherein a confidence level higher than a selected value indicates that the interrogation position is a SNP position associated with the phenotypic characteristic of interest.

97. **(Original)** The method of claim 95, further comprising:

determining the p-value for the interrogation position, wherein a confidence level higher than 99% indicates that the interrogation position is a SNP position associated with the phenotypic characteristic of interest.

98. **(Previously Presented)** The method of claim 1, wherein said interrogation position is at least two different interrogation positions and the step of inputting the first measure includes i) inputting a plurality of first measures corresponding to the different interrogation positions, and the step of inputting the second measure includes ii) inputting a plurality of second measures corresponding to the same interrogation positions as in step i).

99. **(Previously Presented)** The method of claim 98, further comprising:

iii) repeating step i) to obtain another plurality of first measures; and

iv) repeating step ii) to obtain another plurality of second measures.

100. **(Previously Presented)** The method of claim 99, further comprising:

calculating the difference between the plurality of the first measures and the plurality of the second measures for each of the different interrogation positions;

identifying the interrogation positions having a difference above a first threshold value, and the interrogation positions having a difference below a second threshold value between the plurality of the first measures and the plurality of the second measures;

calculating the difference between said another plurality of the first measures and said another plurality of the second measures for each of the different interrogation positions;

identifying the interrogation positions having a difference above the first threshold value, and the interrogation positions having a difference below the second threshold value between said another plurality of the first measures and said another plurality of the second measures,

characterizing those interrogation positions that are identified as having a difference above the first threshold value in both the plurality and said another plurality of measures as being associated with the phenotypic characteristic of interest, and

characterizing those interrogation positions that are identified as having a difference below the second threshold value in both the plurality and said another plurality of measures as being associated with the phenotypic characteristic of interest.

101. **(Original)** The method of claim 100, wherein the first threshold value separates the top 20% in the distribution of the calculated differences from the bottom 95%, and the second threshold value separates the bottom 20% in the distribution of the calculated differences from the top 95%, wherein those interrogation positions that have a difference in the top 20% or the bottom 20% of the distribution of calculated differences are characterized as associated.

102. **(Original)** The method of claim 100, wherein the first threshold value separates the top 5% in the distribution of the calculated differences from the bottom 95%, and the second threshold value separates the bottom 5% in the distribution of the calculated differences from the top 95%, wherein those interrogation positions that have a difference in the top 5% or the bottom 5% of the distribution of calculated differences are characterized as associated.

103. **(Previously Presented)** The method of claim 1, further comprising:
validating the characterization of the interrogation position.

104. **(Original)** The method of claim 103, wherein the step of validating includes identifying a location of the nucleic acid segment in the human genome.

105. **(Original)** The method of claim 104, wherein if the nucleic acid segment is located in a coding or regulatory region of a gene and the interrogation position was designated as associated with the phenotypic characteristic of interest, then the gene is deemed to be associated with the phenotypic characteristic of interest and the step of validating further includes cloning and expressing the associated gene to produce a protein product and characterizing the protein product.

106. **(Original)** The method of claim 104, wherein if the nucleic acid segment is located in a coding or regulatory region of a gene, and the interrogation position was designated as associated with the phenotypic characteristic of interest, then the gene is deemed to be associated with the phenotypic characteristic of interest and the step of validating further includes regulating expression of the associated gene in cells in vitro or in vivo and detecting changes of cells in response to the regulation.

107. **(Original)** The method of claim 104, wherein if the nucleic acid segment is located in a coding or regulatory region of a gene and the interrogation position was designated as associated with the phenotypic characteristic of interest, then the gene is deemed to be associated with the phenotypic characteristic of interest and the step of validating further includes:

screening a library of pharmaceutical candidates against the associated gene or gene product; and

selecting the pharmaceutical candidates that modulate expression of the associated gene or activity of the associated gene product.

108. **(Currently Amended)** A method for determining a relative allele frequency for an interrogation position in a pool of nucleic acid segments based on nucleotide variation at the interrogation position in the nucleic acid segments relative to a reference nucleotide sequence, wherein a nucleic acid segment that is identical to the reference nucleotide sequence at the interrogation position is designated as a reference nucleic acid segment and a nucleic acid segment with a nucleotide variation relative to the reference nucleotide sequence at the interrogation position is designated as an alternate nucleic acid segment, and further wherein the interrogation position contains a biallelic polymorphism, comprising:

determining a plurality of intensities of signals from reference nucleic acid segments in the pool of nucleic acid segments **through one or more assays of one or more determinable markers of the reference nucleic acid segments**, wherein the plurality of intensities of signals from the reference nucleic acid segments are designated as $I_{R,1\text{-}i}$ wherein i is an integer equal to or larger than 2;

determining a plurality of intensities of signals from alternate nucleic acid segments in the pool of nucleic acid segments **through one or more assays of one or more determinable markers of the alternate nucleic acid segments**, wherein the plurality of intensities of signals from the alternate nucleic acid segments are designated as $I_{A,1\text{-}j}$ wherein j is an integer equal to or larger than 2;

determining the relative allele frequency of the interrogation position by calculating an equation of the form:

$< I_{R,1\text{-}i} >/(< I_{A,1\text{-}j} > + < I_{R,1\text{-}i} >)$ or

$< I_{A,1\text{-}j} >/(< I_{A,1\text{-}j} > + < I_{R,1\text{-}i} >)$,

where $<I_{R,1\text{-}i}>$ is the average of the plurality of intensities of signals from the reference nucleic acid segments, and $< I_{A,1\text{-}j} >$ is the average of the plurality of intensities of signals from the alternate nucleic acid segments.

109. **(Original)** The method of claim 108, wherein the signals result at least from perfect match probes on an oligonucleotide array.

110. **(Previously Presented)** The method of claim 108, wherein the average of the plurality of intensities of signals is an arithmetic mean of the plurality of intensities of signals.

111. **(Previously Presented)** The method of claim 108, wherein the average of the plurality of intensities of signals is a trimmed mean of the plurality of intensities of signals.

112. **(Original)** The method of claim 108, wherein the average of the plurality of intensities of signals from the reference nucleic acid segment, $<I_{R,1\text{-}i}>$, excludes outlier signals; and the average of

the plurality of intensities of signals from the alternate nucleic acid segment, $<I_{A,1\text{-}j}>$, excludes outlier signals.

113. **(Original)** The method of claim 108, wherein at least one of $<I_{R,1\text{-}i}>$ or $<I_{A,1\text{-}j}>$ is corrected.

114. **(Original)** The method of claim 113, wherein at least one of $<I_{R,1\text{-}i}>$ or $<I_{A,1\text{-}j}>$ is corrected for background.

115. **(Original)** The method of claim 114, wherein at least one of $<I_{R,1\text{-}i}>$ and $<I_{A,1\text{-}j}>$ are corrected for background and the relative allele frequency of an interrogation position is determined by calculating an equation of the form:

$$\frac{(<I_R^{pm}>-\frac{<I_R^{mm}>+<I_A^{mm}>}{2})}{(<I_A^{pm}>-\frac{<I_R^{mm}>+<I_A^{mm}>}{2})+(<I_R^{pm}>-\frac{<I_R^{mm}>+<I_A^{mm}>}{2})}$$

wherein $<I_R^{pm}>$ is the average of the plurality of intensities of signals from the reference nucleic acid segment generated by perfect match probes on an oligonucleotide array; $<I_A^{pm}>$ is the average of the plurality of intensities of signals from the alternate nucleic acid segment generated by perfect match probes on the oligonucleotide array; $<I_R^{mm}>$ is the average of the plurality of intensities of signals from the reference nucleic acid segment generated by mismatch probes on the oligonucleotide array; and $<I_A^{mm}>$ is the average of the plurality of intensities of signals from the alternate nucleic acid segment generated by mismatch probes on the oligonucleotide array.

116. **(Withdrawn)** The method of claim 115, wherein the average of intensities of signals is an arithmetic mean of intensities of signals.

117. **(Original)** The method of claim 115, wherein the average of intensities of signals is a trimmed mean of intensities of signals.

118. (**Previously Presented**) A computer-implemented method for characterizing a polymorphic marker in a nucleic acid as being associated with a phenotypic trait of interest, comprising:

inputting into a computer system a first measure of relative allele frequency for the polymorphic marker in a first sample, said first sample containing nucleic acids from a first group of n individuals, wherein n is an integer equal to or larger than 2;

inputting into a computer system a second measure of relative allele frequency for the polymorphic marker in a second sample, said second sample containing nucleic acids from a second group of m individuals, wherein m is an integer equal to or larger than 2;

analyzing in the computer system the first measure and the second measure to characterize the polymorphic marker; and

outputting a result of said analyzing, wherein the result characterizes the interrogation position as being associated with the phenotypic trait of interest.

119. **(Withdrawn)** A computer-implemented method for characterizing an interrogation position in a nucleic acid segment, comprising:

inputting into a computer system a group of first measures of hybridization probe intensities corresponding to the interrogation position in the nucleic acid segment derived from a first sample collected from a case group of n individuals, wherein n is an integer equal to or larger than 2;

calculating in the computer system a group of first relative allele frequencies at the interrogation position for the case group based on the group of first measures of hybridization probe intensities;

inputting into the computer system a group of second measures of hybridization probe intensities corresponding to the interrogation position in the nucleic acid segment derived from a second sample collected from a control group of m individuals, wherein m is an integer equal to or larger than 2;

calculating in the computer system a group of second relative allele frequencies at the interrogation position for the control group based on the group of second measures of hybridization probe intensities;

analyzing in the computer system the group of the first relative allele frequencies and the group of second relative allele frequencies to characterize the interrogation position as being associated with a phenotypic characteristic of interest.

120. **(Withdrawn)** The method of claim 119, wherein the group of the first measures of hybridization probe intensities are obtained by at least 2 sets of repetitive experiments, and the group of the second measures of hybridization probe intensities are obtained by at least 2 sets of repetitive experiments.

121. **(Withdrawn)** The method of claim 119, wherein the step of analyzing includes:

calculating a mean of the group of the first relative allele frequencies;

calculating a mean of the group of the second relative allele frequencies; and

calculating the absolute difference between the mean of the group of the first relative allele frequencies and the mean of the group of the second relative allele frequencies,

where if the absolute difference is equal to or above a predetermined threshold value, the interrogation position is characterized as being associated with the phenotypic characteristic of interest.

122. **(Withdrawn)** The method of claim 121, wherein the threshold value ranges from 0.02 to 0.2.

123. **(Withdrawn)** The method of claim 121, wherein the threshold value ranges from 0.04 to 0.1.

124. **(Withdrawn)** The method of claim 119, wherein the step of analyzing includes applying a statistical test to the group of the first relative allele frequencies and the group of second relative allele frequencies to characterize the interrogation position as being associated with a phenotypic characteristic of interest.

125. **(Withdrawn)** The method of claim 124, wherein the statistical test is a t-test or rank-sum test.

126. **(Withdrawn)** The method of claim 119 wherein said an interrogation position is at least two interrogation positions, and further comprising:

calculating the difference between the group of the first measures and the group of the second measures for each of the different interrogation positions;

characterizing the interrogation positions having a difference above a first threshold value, and interrogation positions having a difference below a second threshold value between the group of the first measures and the group of the second measures as associated with the phenotypic characteristic of interest.

127. **(Withdrawn)** A computer-implemented method for characterizing an interrogation position in a nucleic acid segment with a previously known location in the human genome, comprising:

inputting into a computer system a first measure of relative allele frequency at the interrogation position in the nucleic acid segment derived from a first sample collected from a first group of n individuals, wherein n is an integer equal to or larger than 2;

inputting into the computer system a second measure of relative allele frequency at the interrogation position in the nucleic acid segment derived from a second sample collected from a second group of m individuals, wherein m is an integer equal to or larger than 2; and

analyzing in the computer system the first measure and the second measure to characterize the interrogation position.

128. **(Withdrawn)** The method of claim 127, wherein analyzing includes analyzing in the computer system the first measure and the second measure to characterize the interrogation position as being associated with a phenotypic characteristic of interest.

129. **(Withdrawn)** The method of claim 128, wherein the nucleotide segment is proximal to or within a region of a candidate gene that is not previously known to be associated the phenotypic characteristic of interest.

130. **(Withdrawn)** The method of claim 128, wherein the nucleotide segment is proximal to or within a region of a candidate gene that is previously suspected of being associated the phenotypic characteristic of interest.

131. **(Withdrawn)** The method of claim 128, wherein the nucleotide segment is proximal to or within an untranslated region of a candidate gene that is not previously known to be associated the phenotypic characteristic of interest.

132. **(Withdrawn)** The method of claim 128, wherein the nucleotide segment is proximal to or within an untranslated region of a candidate gene that is previously suspected of being associated the phenotypic characteristic of interest.

133. (**Currently Amended**) Data processing apparatus for characterizing an interrogation position in a nucleic acid segment, wherein the interrogation position contains a biallelic polymorphism, comprising:

a data processor; and

a storage device holding computer readable code in communication with the data processor, the computer readable code including:

computer code which determines a first measure of relative allele frequency at the interrogation position in the nucleic acid segment derived from a first **pooled** sample collected from a case group of n individuals, wherein n is an integer equal to or larger than 2, **[[and]]** wherein the individuals in the case group are selected based on a phenotypic characteristic of interest**, and wherein said first measure of relative allele frequency is derived from intensity signals from a first probe set**;

computer code which determines a second measure of relative allele frequency at the interrogation position in the nucleic acid segment derived from a second **pooled** sample collected from a control group of m individuals, wherein m is an integer equal to or larger than 2, **[[and]]** wherein the individuals in the control group are selected based on lack of the phenotypic characteristic of interest; **and wherein said second measure of relative allele frequency is derived from intensity signals from a second probe set** and

computer code which analyzes the first measure and the second measure to characterize the interrogation position as being associated with the phenotypic characteristic of interest.

134. **(Cancelled)**

135. **(Previously Presented)** The data processing apparatus of claim 133, wherein the data processing apparatus is further in communication with another data storage device which stores a first measure of the intensity of signals from a first probe set on an oligonucleotide array and a second measure of the intensity of signals from a second probe set on the oligonucleotide array, wherein the first measure of relative allele frequency is determined based on the first measure of intensity and the second measure of relative allele frequency is determined based on the second measure of intensity.

136. **(Original)** The data processing apparatus of claim 135, wherein the data processing apparatus is further in communication with an imaging device.

137. **(Original)** The data processing apparatus of claim 136, wherein the imaging device is a scanner that determines the first measure of intensity and the second measure of intensity.

138. **(Currently Amended)** A computer program product comprising a machine readable medium on which is provided program instructions for characterizing an interrogation position in a nucleic acid segment, wherein the interrogation position contains a biallelic polymorphism, comprising:

code for determining a first measure of relative allele frequency at the interrogation position in the nucleic acid segment derived from a first **pooled** sample collected from a case group of n individuals, wherein n is an integer equal to or larger than 2, **[[and]]** wherein the individuals in the case group are selected based on a phenotypic characteristic of interest**, and wherein said first measure of relative allele frequency is derived from intensity signals from a first probe set**;

code for determining a second measure of relative allele frequency at the interrogation position in the nucleic acid segment derived from a second **pooled** sample collected from a control group of m individuals, wherein m is an integer equal to or larger than 2, **[[and]]** wherein the individuals in the control group are selected based on lack of the phenotypic characteristic of

interest**, and wherein said second measure of relative allele frequency is derived from intensity signals from a second probe set**; and

code for analyzing the first measure and the second measure to characterize the interrogation position as being associated with a phenotypic characteristic of interest.

139. **(Cancelled)**

140. **(New)** The method of claim 1, wherein the first probe set and/or the second probe set comprises a probe designed to interrogate the interrogation position.

141. **(New)** The method of claim 140, wherein the probe hybridizes directly to the nucleic acid segment.